COMPARATIVE ASSESSMENT OF SEVERE PEDIATRIC TBI MANAGEMENT BETWEEN DEVELOPED AND DEVELOPING COUNTRY INSTITUTIONS: A STUDY COMPARING PHOENIX, ARIZONA TO NEIVA, COLOMBIA

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Laeth George
Class of 2019

Mentor: P. David Adelson, MD

ACKNOWLEDGEMENTS

Thank you to all the faculty and staff at Phoenix Children's Hospital who helped make this work possible. Special thanks to Danni Brown for helping at every step in the research process, as well as Dr. Adelson for his continued mentorship and guidance.

ABSTRACT

Background and Significance

Close monitoring and timely intervention improve survival and functional outcomes in severe traumatic brain injury (TBI), but their availability depends on institutional and national resources. Barrow Neurological Institute at Phoenix Children's Hospital, USA (BPCH) and the University Hospital in Neiva, Colombia (NUH) compared the management and outcomes of pediatric patients with severe TBI over a 5-year period.

Methods

Retrospective chart review identified children aged 0 to 17 years with severe TBI admitted to BPCH and NUH. Data collected included demographics, Glasgow Coma Scores (GCS), pre- and post-admission management, mortality, and Glasgow Outcome Scores (GOS). Comparisons employed the Pearson Chi-square, Fisher exact, T-test or Wilcoxon-rank sum test, as appropriate.

Results

A total of 101 subjects met inclusion criteria (66 BPCH and 35 NUH). Study populations were similar in age, gender, and admission GCS (μ 5 SD + 2). Cause and mechanism of injury varied between centers (p=0.000 and p=0.004), as did time from injury to arrival at the treating hospital (p=0.025). BPCH had a higher incidence of intracranial hemorrhages, whereas NUH had a higher incidence of diffuse axonal injury. NUH employed invasive monitoring less frequently than BPCH (5/35 v. 45/66; p=0.000). The use of surgical decompression and subdural evacuation was higher at BPCH (p=0.031 and p=0.003). Overall mortality rates were similar between institutions (15 % BPCH, 17% NUH) as were functional outcomes with low-to-moderate disability (52% BPCH, 54% NUH), and days of hospital (μ 33 BPCH, 28 NUH) and ICU utilization (12 BPCH, 13 NUH).

Conclusions

Despite variation in resource availability, monitoring capacity/utilization, and therapeutic approaches, there were no significant differences in survival and overall functional outcomes between study populations.

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION AND SIGNIFICANCE

Traumatic Brain Injury (TBI) is an etiologically heterogeneous condition that represents a global public health issue with major socioeconomic impact [1]. Murray and Lopez found that, from the current global population, 57 million people have been hospitalized due to TBI at some point in their lives, and at least 10 million of those events have been severe enough to result in death or require hospitalization [2]. In the United States, pediatric TBI alone is estimated to have caused approximately 1,484 deaths, 17,930 hospitalizations and 641,935 emergency department visits in 2013 [3]. While epidemiological data on pediatric TBI in Latin America is limited, it is known that TBI-associated death rates are in excess of 75 per 100,000 in Latin America, and ascend to 125 per 100,000 in Colombia [4]. In Medellin, a major city in Colombia, TBI is the main cause of death in children [5].

Evidence-based guidelines exist for the treatment of severe pediatric TBI. The Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents were initially published in 2003 and most recently revised in 2012 by the Brain Trauma Foundation [6-7]. However, there are several elements that may impact the effectiveness of the proposed treatment strategies [8-10]. As resource limitations in developing countries are a major constraint to evidence-based care and effective decision making, the influence of these elements may vary from the developed to the developing world. There is a need to conduct research to identify these differences and their impact on care. With adequate research support, policies and guidelines can be adapted for use in resource-limited settings, optimizing benefits in low- and middle-income countries (LMICs) [11].

In this study, we performed a retrospective review of pediatric patients with severe TBI in two tertiary, pediatric hospitals in the United States and Colombia, comparing characteristics, management and outcomes.

MATERIALS AND METHODS

Our team performed a retrospective chart review of patients' ages 0 to 17 years, who presented to Phoenix Children's Hospital (PCH), US and the Hospital Universitario de Neiva, Colombia with a diagnosis of severe TBI during the five-year period between July 1, 2010 and July 31, 2015.

We defined severe TBI as a reported or evidenced mechanical insult to the brain where the patient presented with an admission GCS of 8 or less.[16] The study enrollment criteria included: age 0 to <18, diagnosis of TBI, GCS of 8 or less at admission and the absence of preexisting conditions affecting neurological function.

In PCH, subjects were identified by querying the electronic medical records system for diagnostic codes corresponding to TBI. Subject selection and data collection were performed concomitantly; data collection involved the extraction of information from several different medical record systems. The PCH Institutional Review Board approved this study under expedited review.

The NUH research team identified subjects by searching the electronic medical record of the hospital pediatric intensive care unit (ICU) for diagnostic codes corresponding to TBI. Subjects were then screened for inclusion using the above criteria. Researchers used a data collection form to extract patient information from the medical record. This data was deidentified, compiled in a research record, and shared with PCH for analysis. This research was approved by the university hospital ethical review board.

At both institutions, extracted data included patient identifiers, demographics, information about the TBI event, hospital admission and management, imaging assessment, and outcomes data. The PCH team analyzed deidentified data from both institutions using SPSS (Chicago, IL). Comparisons employed the Pearson Chi-square, Fisher exact, Kruskal-Wallis, t-test or Wilcoxon-rank sum test, as appropriate.

RESULTS

Demographics

In total, sixty-six patients (34 male, 32 female) from PCH and 35 patients (24 male, 11 female) from NUH met criteria for inclusion in the study. The mean ages at PCH and Neiva were 7.77 and 6.59, respectively (Table 1). Mean incoming GCS was similar between the two groups (5.42 at PCH and 5.46 at Neiva). The primary cause of injury at Neiva was motor vehicle accidents (65.7%), while accidental falls (31.8%) and motor vehicle accidents (MVA, 21.2%) were the main causes of injury at PCH. At PCH, most patients (62.1%) were transferred directly to the study hospital from the scene of injury. In contrast, just 17.1% of patients were transferred directly from the scene of injury in Colombia, while 80% of patients were transferred from another hospital. Time from injury to arrival at the treating hospital was significantly longer in Neiva (p=0.035). Cause and mechanism of injury varied between institutions (p 0.000 and 0.004). As seen in Table 1, the most common trauma-associated injuries at PCH were external (39.4%), lower extremity (22.7%), and upper extremity (19.7%) in nature. At Neiva, the most common trauma-associated injuries were facial (35.8%), upper, and lower extremity (20.1% each).

Patients with severe TBIs were subject to an initial head computer tomography (CT) scan on admission to assess potential internal damage. As seen in Table 1, common findings on CT at PCH were skull fracture (65.2%), subdural hematomas (54.5%), and contusions (51.5%). At Neiva, the common findings included skull fracture (74.3%), diffuse axonal injury (45.7%), and a midline shift (28.6%). The identification of radiological abnormalities significantly differed between institutions. Notable differences include a higher incidence of subdural hematomas (54.5% v. 11.4%, p=0.001) in the PCH cohort and a higher rate of diffuse axonal injuries (45.7% vs. 15.2%, p=0.002) in the Neiva cohort (Table 1).

Management

Hyperosmolar therapy was used in many of the patients at both study hospitals. PCH used hypertonic saline on 48.5% of studies patients and mannitol on 40.9% of patients, while Neiva used hypertonic saline on 80% of studied patients, and mannitol on 51.5%.

Table 1: Demographic and clinical characteristics of patients at PCH and Neiva trauma centers.

Characteristic	Location		P-value
	PCH N=66	**Neiva N=35**	
Age (years)			
Mean (SD)	7.77 (5.36)	6.60 (4.05)	0.42*
Median (Q1, Q3)	6.80 (3.25, 12.78)	6.42 (3.74, 8.40)	
Sex, N (%)			
Female	32 (48)	11 (31)	0.14‡
Male	34 (52)	24 (69)	
Glasgow Coma Scale *Mean (SD)*	5.42 (2.16)	5.46 (2.24)	0.37‡
Associated injuries, N (%)			
Face	10 (15)	12 (34)	0.04‡
Neck	6 (9)	0 (0)	0.09‡
Abdomen	10 (15)	3 (9)	0.53‡
External	26 (39)	2 (6)	0.0003‡
Lower Extremities	15 (23)	6 (17)	0.61‡
Upper Extremities	13 (20)	7 (20)	1.00‡
Spine	4 (6)	3 (9)	0.69‡
Thorax	12 (18)	6 (17)	1.00‡
None	21 (32)	2 (6)	0.002‡
Number of Associated injuries			
None	21 (32)	2 (7)	0.002‡
1	14 (21)	15 (56)	
2	11 (17)	6 (22)	
3	20 (30)	4 (15)	
Missing N= 8			
Cisterns and Midbrain, N (%)			
Collapsed	7 (11)	1 (3)	0.01‡
Open	39 (59)	28 (88)	
Partially Open	20 (30)	3 (9)	
Midline Shift, N (%)	20 (30)	10 (29)	1.00‡
Skull Fracture, N (%)	43 (65)	26 (74)	0.38‡
Subdural Hematoma, N (%)	36 (55)	4 (11)	<0.0001‡
Subarachnoid Hemorrhage, N (%)	28 (42)	7 (20)	0.03‡
Intraparenchymal Hematoma, N (%)	22 (33)	5 (14)	0.06‡
Intraventricular Hemorrhage, N (%)	13 (20)	0 (0)	0.004‡
Diffuse Axonal injury, N(%)	10 (15)	16 (46)	0.002‡

*P-value from Kruskal-Wallis test, ‡P-value from Fisher-exact test

Seizure incidence in the immediate (less than 24 hours post-injury), early (days 2-7 post-injury), and late (greater than 7 days post-injury) were similar in both cohorts. PCH saw an incidence of immediate seizures in 28.8% of patients, early seizures in 28.8%, and late seizures in 6.1%. Neiva saw a rate of 28.6%, 25.7%, and 5.7%, respectively. Seizure prophylaxis differed dramatically between the two institutions. At PCH, the most common seizure prophylaxis administered was fosphenytoin and levetiracetam (30.3% and 34.8%, respectively). Neiva administered phenytoin as prophylaxis for 85.7% of patients. Consequently, seizure management differed as well, with levetiracetam being used most frequently at PCH vs. valproic acid at Neiva.

As seen in table 2¸ PCH was more aggressive with interventions. 56.1% of patients at PCH had an external ventricular drain (EVD) placed, compared to 0% of patients at Neiva. Neiva also did not monitor intraparenchymal temperature or tissue oxygen pressure. Surgical management between the two institutions differed as well (Table 2). PCH was more invasive, with 25.8% of patients receiving a unilateral decompressive craniectomy (vs. 5.7% in Neiva) and 21.2% of patients receiving a subdural evacuation (vs. 0% in Neiva).

Outcomes

Outcomes between the two cohorts were similar, as seen in Table 2. The majority of patient courses at both PCH and Neiva resulted in low disability (51.5% and 54.3%, respectively, $p = 0.56$) with similar rates of death (15.1% and 17.1%, respectively, $p = 0.56$). Length of stay (LOS) in the ICU were similar as well.

Table 2: Treatments and outcomes for patients at PCH and Neiva trauma centers.

Treatments	**Location**		**P-value**
	PCH N=66	**Neiva** N=35	
Decompressive Craniectomy, N (%) Bifrontal Unilateral None	4 (6) 17 (26) 45 (68)	1 (3) 2 (6) 32 (91)	0.02‡
Subdural evacuation, N (%)	14 (21)	0 (0)	0.002‡
Epidural evacuation, N (%)	5 (8)	2 (6)	1.00‡
Intraparenchymal evacuation	5 (8)	2 (6)	1.00‡
Outcomes			
Glasgow Outcome Scale 1. Death 2. Persistent Vegetative State 3. Severe Disability 4. Moderate Disability 5. Low Disability *Missing N=4*	 10 (15) 3 (5) 18 (28) 16 (25) 18 (28)	 6 (19) 0 (0) 7 (22) 4 (12) 15 (47)	0.26‡
Outcome Categories Dead Severe Disability Low Disability *Missing N=4*	 10 (16) 21 (32) 34 (52)	 6 (19) 7 (22) 19 (59)	0.56‡
Hospital Length of Stay (days) *Mean (SD)* *Median (Q1, Q3)*	 33 (44) 20 (8,43)	 27 (34) 17 (8, 32)	0.32*
ICU Length of stay *Mean (SD)* *Median (Q1, Q3)*	 12 (13) 8 (4,14)	 13 (25) 5 (3, 11)	0.09*

*P-value from Kruskal-Wallis test

‡P-value from Fisher-exact test

DISCUSSION

This data demonstrates several dissimilarities in the epidemiology and management of traumatic brain injury between PCH in Phoenix, Arizona, USA and the Hospital Universitario de Neiva, Colombia, including patient demographics, mechanism of injury, and type of injury on CT imaging. Mean age of injury and Glasgow Coma Scale (GCS) at intake were similar in both groups, although patients at Neiva were more likely to be male. Glasgow Coma Scale and mortality are similar to that seen in other published studies of pediatric TBI globally. The high preponderance of diffuse axonal injury on CT and higher prevalence of facial fractures seen on CT in patients in Colombia may be due to the frequency of road traffic collisions as the mechanism of injury.

The most striking differences between the two cohorts related to management of patients with TBI. The majority of pediatric patients at PCH were transported directly to the hospital from the site of injury. In contrast, only a small proportion of patients seen at Neiva were brought directly to the hospital; most were transferred from another institution. Rates of operative management differed between groups as well, with patients at PCH being more likely to receive intracranial pressure monitoring and to undergo operative management. Outcomes, including death and disability, were similar between the two groups, although mean hospitalization days were greater in Neiva and the proportion of patients with severe disability at discharge was higher at PCH.

Despite these differences in injury mechanism, time to treatment, radiologic findings and surgical management, we found no significant differences in death and functional outcome between patients treated for severe TBI at Phoenix Children's Hospital (PCH), US and the Hospital Universitario de Neiva, Colombia. Mortality rates were similar between institutions (15 % BPCH, 17% NUH) as were functional outcomes with low to moderate disability (52% BPCH, 54% NUH). Hospital and ICU length-of-stay were also similar between locations (μ 33 BPCH, 28 NUH and 12 BPCH, 13 NUH) (Table 2).

As discussed earlier, pediatric TBI guidelines were published by the Brain Trauma Foundation, and most recently revised in 2012. The original guidelines, published in 2003, were associated with improved outcomes once a standardized care plan based on the above guidelines was established, as demonstrated by Pineda et al [12]. Outcomes were defined using Glasgow Outcome Scale, as used in this study. Similarly, after the revision in 2012, a study by O'Lynnger et al demonstrated that, following standardization and adoption of a protocol based on the 2012 guidelines, outcomes in similar pediatric patients improved [13]. Similar studies have replicated these findings in the adult TBI literature [14]. While few in number, the studies suggest that adoption of a protocol-driven management plan in the ICU setting improves outcomes in pediatric patients with TBIs.

This study uses developed and developing countries as comparators partially as a surrogate for the consideration of resource availability and utilization. Costs were not directly measured in this study. However, hospital length of stay has been used and validated as a surrogate for resource utilization [15]. Notably, there were no statistically significant differences in both hospital and ICU LOS between PCH and Neiva. However, as discussed earlier, invasive management in the form of ICP monitoring and operative interventions were significantly more common at PCH relative to Neiva. This trend is suggestive of increased resource utilization by PCH when compared to Neiva independent of LOS, which resulted in statistically similar outcomes at time of discharge.

FUTURE DIRECTIONS

Future studies can be directed at broadening the diversity of clinical sites beyond PCH and Neiva, to see if the findings here are reproducible in similar peer institutions or are an isolated finding. Other avenues of research include analysis directed specifically at whether or not adherence to all components of pediatric TBI guidelines improves mortality in these differing, global patient populations, and whether or not certain guidelines are more impactful than others in these different patient subgroups.

CONCLUSIONS

In sum, several important differences exist in the management and epidemiology of severe traumatic brain injury at two institutions in the developed and developing world. Additional studies are necessary to see how widespread these differences are and whether there are regional differences in acute management of pediatric TBI. However, this study highlights the importance of adherence to evidence-based practice. Although this is observational, it is the first evaluation of acute management of severe TBI in pediatric patients in Latin America and a robust comparison of actual practice in the developed and developing world.

REFERENCES

1. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation 2007;22:341-353.
2. Murray CJ, Lopez AD. Global Health Statistics: A Compendium of Incidence, Prevalence and Mortality Estimates for Over 200 Conditions. Cambridge, MA: Harvard School of Public Health; 1996.
3. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. MMWR Surveill Summ. 2017 Mar 17;66(9):1-16.
4. Santacruz LF and Herrera AM. Trauma Craneoencefalico. Abordaje Inicial en los Servicios de Urgencias, Chapter 12, pp. 233-55.
5. Correa MA, González G, Herrera MH, Orozco A. Epidemiología del trauma pediátrico en Medellín, Colombia, 1992-1996. Colombia Med 2000; 31: pp. 77-80. Accessed at http://colombiamedica.univalle.edu.co/Vol31No2/trauma.html.
6. Adelson PD, Clyde B, Kochanek PM, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Pediatr Crit Care Med. 2003; 4 (Suppl 3): S1-75.
7. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children and adolescents: second Edition. Pediatr Crit Care Med. 2012; 13 (Suppl 1):S1–82.
8. Adelson PD, Pineda J, Bell MJ, et al. Common data elements for pediatric traumatic brain injury: recommendations from the working group on demographics and clinical assessment. J Neurotrauma. 2012; 29(4):639–53.
9. O'Lynnger TM, Shannon CN, Le TM, Geeno A, Chung D, Lamb FS, Wellons JC. Standardizing ICU management of pediatric traumatic brain injury is associated with improved outcomes at discharge. J Neurosurg Pediatr. Published online October 9, 2015; DOI: 10.3171/2015.5.PEDS1544.

10. Vavilala MS, Kernic MA, Wang J, Kannan N, Mink RB, Wainwright MS, Groner JI, Bell MJ, Giza CC, Zatzick DF, et al. Acute Care Clinical Indicators Associated With Discharge Outcomes in Children With Severe Traumatic Brain Injury. Crit Care Med. 2014; 42(10):2258–66.
11. Harris OA, Bruce CA, Reid M, Cheeks R, Easley K, Surles MC, Pan Y, Rhoden-Salmon D, Webster D, Crandon I. Examination of the management of traumatic brain injury in the developing and developed world: focus on resource utilization, protocols and practices that alter outcome. J Neurosurg. 2008;109:433-438.
12. Pineda JA, Leonard JR, Mazotas JG, Noetzel M, Limbrick DD, Keller MS, Gill J, Doctor A. Effect of implementation of a paediatric neurocritical care programme on outcomes after severe traumatic brain injury: a retrospective cohort study. Neurology 2013; 12(1):45-42.
13. O'Lynnger TM, Shannon CN, Le TM, Greeno A, Chung D, Lamb FS, Wellons JC. Standardizing ICU management of pediatric traumatic brain injury is associated with improved outcomes at discharge. J Neurosurg Pediatr 2016; 17(1); 19-26.
14. Fakhry SM, Trask AL, Waller MA, Watts DD; IRTC Neurotrauma Task Force. Management of brain-injured patients by an evidence-based medicine protocol improves outcomes and decreases hospital charges. J Trauma. 2004 Mar;56(3):492-499.
15. Newgard CD, Fleischman R, Choo E, Ma OJ, Hedges JR, McConnell KJ. Validation of length of hospital stay as a surrogate measure for injury severity and resource use among injury survivors. Acad Emerg Med. 2010 Feb;17(2):142-150.